CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214487Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214487
PDUFA Goal Date	October 7, 2021
OSE RCM #	2020-1484
Reviewer Name(s)	Theresa Ng, PharmD, BCPS
Team Leader	Laura Zendel, PharmD, BCPS
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 6, 2021
Subject	Evaluation of Need for a REMS
Established Name	Avacopan
Trade Name	Tavneos
Name of Applicant	ChemoCentryx Inc
Therapeutic Class	Selective Complement 5a (CD88) receptor antagonist
Formulation(s)	10 mg Oral capsule
Dosing Regimen	30 mg twice daily with food

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tavneos (avacopan) is necessary to ensure the benefits outweigh its risks. ChemoCentryx Inc. (ChemoCentryx) submitted a New Drug Application (NDA) 214487 for avacopan with the proposed indication for the treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). The Applicant included a proposed risk management plan that consisted of routine pharmacovigilance and labeling. The indication was revised "as an adjunctive treatment of adult patients with severe active ANCA-associated vasculitis (GPA and MPA) in combination with standard therapy including GCs. It does not eliminate GC use" during the review cycle to better reflect the treatment population and background therapy, as supported by the data from the pivotal phase 3 study.

ANCA-associated vasculitis (AVV) is a rare multisystem autoimmune disease with high morbidity and mortality if untreated. Even with current treatment, an estimated 11% of patients die within the first year of diagnosis, with most deaths related to treatment. The efficacy of avacopan for AVV was evaluated in a pivotal phase 3 study (Study CL010_168). Although, the phase 3 study findings met the primary endpoint of remission rates (superiority at week 52), the clinical and statistical reviewers are recommending a complete response. They concluded that the Applicant did not provided confirmatory evidence to support the reliance on a single study to provide substantial evidence of effectiveness for the proposed indication for the treatment of AVV (GPA and MPA). Division Director for DRTM acknowledges the concerns identified by the clinical and statistical reviewers; however, they determined there is sufficient information to conclude that the benefit-risk profile is favorable for approval of avacopan for the treatment of adults with severe active AAV. The Office Director concurs with the Division Director's recommendation.

The major risks associated with avacopan are hepatotoxicity and hypersensitivity including angioedema. The phase 3 study identified four cases of probable or highly likely drug-induced liver injury (DILI) with one identified Hy's Law case in the avacopan arm. However, the DILI reviewer could not conclude with confidence of the role of avacopan and liver toxicity due to confounding therapies in AVV patient with potentially hepatotoxic effects. Animal studies did not demonstrate significant liver toxicity and the mechanism for hepatotoxicity associated with avacopan is not known. The phase 3 study also identified imbalance incidences of hypersensitivity, particularly, angioedema. However, due to the small safety database, no conclusion can be made, and further studies are needed to further characterize this risk.

The review team from DRM and the Division of Rheumatology and Transplant Medicine (DRTM) determined a REMS is not needed to ensure the benefits of avacopan outweigh its risks. The primary prescribing population are rheumatologists but may include other specialists such as neurologists, nephrologists, pulmonologists, dermatologists, and urologists, who are experienced in treating patients with AVV. Consistent with other immunosuppressive therapies for AVV such as with cyclophosphamide and methotrexate, labeling will convey the risks of hepatotoxicity (including recommendations for monitoring of liver testing) and hypersensitivity/ angioedema (Section 5: Warnings and Precautions and

Section 2: Dosing and Administration). The Agency will require a postmarketing study to provide additional safety data to characterize the risks, particularly, hepatotoxicity and angioedema and a postmarketing commitment to further evaluate the treatment benefit of avacopan to better inform on the role of avacopan in clinical practice.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tavneos (avacopan or CCX168) is necessary to ensure the benefits outweigh its risks. ChemoCentryx Inc. (ChemoCentryx) submitted a New Drug Application (NDA) 214487 for avacopan with the proposed indication for the treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). Subsequent to discussions on the adequacy of the efficacy and safety data of avacopan in the May 6, 2021 Arthritis Advisory Committee meeting, the Applicant agreed to a revised indication statement to better reflected the treatment population and background therapy, as supported by the data from the pivotal trial. The indication for avacopan was revised to "as an adjunctive treatment of adult patients with severe active ANCA-associated vasculitis (GPA and MPA) in combination with standard therapy including glucocorticoids (GCs). It does not eliminate GC use". This application is under review in the Division of Rheumatology and Transplant Medicine (DRTM). The Applicant included a risk management plan consisting of routine pharmacovigilance and labeling.

2 Background

2.1 Product Information

Tavneos (avacopan or CCX1688) is a new molecular entity (NME)[a] that antagonizes the binding of complement 5a (C5a) to its receptor (i.e., C5aR antagonist). The proposed indication is as an adjunctive treatment of adult patients with severe active ANCA-associated vasculitis (GPA and MPA) in combination with standard therapy including GCs. It does not eliminate glucocorticoids (GC) use. C5a and C5aR may play a central role in the pathogenesis of ANCA-associated vasculitis (AVV). C5a is a terminal component of the complement cascade involved with proinflammatory effects such as neutrophil activation and migration, adherence to sites of small blood vessel inflammation, and vascular endothelial cell retractions and increased permeability. Avacopan inhibits binding of complement 5a (C5a) to its receptor, thus preventing C5a's downstream effects of enhancing inflammation by priming neutrophils and other cells involved in the inflammatory response. The proposed dosage is 30 mg (three 10 mg capsules) twice daily taken with food and is proposed for chronic use in the outpatient setting to achieve and maintain remission in patients with AAV.[b] Avacopan is not marketed in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for avacopan (NDA 21448) relevant to this review:

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

- 5/19/2014: Orphan drug designation granted for avacopan (IND 120784) for ANCA-associated vasculitis.
- 03/19/2020: In a Pre-NDA meeting, the Agency conveyed their concerns on the complexity of study designs and the challenge in the interpretation of a clinically meaningful benefit of avacopan, clinical relevance of results and intended use in clinical practice, assessment outcomes parameters, pooling of safety data, and the possibility of Advisory Committee (AC) Meeting.
- 07/07/2020: ChemoCentryx submitted NDA 214487 for the treatment of ANCA-associated vasculitis (AVV).
- 12/14/2020: The Agency held a Mid-Cycle Meeting (MCM) with the Applicant. No major safety concerns were discussed, and there were no discussions of any plans for a REMS.
- 05/06/2021: The Agency convened an Arthritis Advisory Committee (AAC) Meeting to discuss NDA 214487.[1,2] Its primary purpose is to seek input from vasculitis specialists and researchers on whether avacopan's data provide substantial evidence of efficacy and overall benefit-risk in the proposed indication for the treatment of AAV (GPA and MPA). Overall, the committee members split on determining the adequacy of the efficacy, safety, and overall benefit-risk profile of avacopan. A REMS proposal was not discussed. (*See appendix 10.4 for a summary of ACC voting results.)*
- 5/18/2021: The Agency issued an information request (IR) to the Applicant expressing continued concerns on the adequacy of the data to support the proposed indication and the use of avacopan to reduce or eliminate GCs based on the data in the NDA submission.[3] The Agency asked the Applicant to consider how the AAC discussion impacts the proposed indication and how the data from the clinical program may inform the use of avacopan for labeling.
- 6/21/2021: The Applicant submitted a clinical information amendment to provide additional safety data, a proposed post-approval clinical trial, and a revised indication statement.[4] In addition, the amendment further addressed the Agency's concerns on efficacy and safety discussed during the AAC meeting.
- 7/1/2021: The review team informed the Applicant of their disagreement of the revised indication in the clinical information amendment, dated 6/21/2021, as it did not adequately address the Agency's concerns and the discussions from the AAC.[5] To continue the labeling review, the Agency provided a revised indication statement:

  > "as an adjunctive treatment of adult patients with ANCA-associated vasculitis (GPA and MPA) in combination with standard therapy including GCs. It does not eliminate GC use."

  In addition, the Agency also provided revised data presentation format in labeling for the Applicant to consider.

- 7/14/2021: The Applicant agreed to the Agency's proposed revisions to the indication statement and data presentation in labeling.[6]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

ANCA-associated vasculitis (AVV) is a rare multisystem autoimmune disease manifesting as necrotizing vasculitis of the small and medium-sized blood vessels of various body systems such as neurologic, pulmonary, cardiac, and renal. AVV is commonly associated with circulating antineutrophil cytoplasmic antibody (ANCA). The two main forms of AVV are granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The prevalence of AAV is 200-400 cases per million people.[7] The peak age of onset of AVV is 65-74 years, and is very rare in childhood. Most studies suggest a slightly higher occurrence in men than women.[8] GPA is more common in patients of European ancestry while MPA is more common in patients from Eastern Asia.[7,c]

AVV may present with a spectrum of disease severity and symptoms, ranging from skin manifestations to glomerulonephritis to life-threatening pulmonary hemorrhage. If left untreated, 80% of patients with GPA or MPA die within 2 years of disease onset.[9d] It is estimated that 11% of patients die within the first year after diagnosis and most deaths (59%) are attributable to the medications used followed by disease related deaths (14%), primarily due to infection (48%).[10,11]

3.2 Description of Current Treatment Options

There is no cure for AAV, but there are treatments available to manage the condition. The 2015 updated European League Against Rheumatism (EULAR) along with the European Renal Association (ERA) – European Dialysis and Transplant Association (EDTA), or EULAR/ERA-EDTA, provides evidence-based recommendations for the management of AVV.[12] The goal is to induce and maintain long-term remission. The choice of therapy depends on extent of organ involvement and the patient's treatment phase (i.e., induction or maintenance). Induction usually requires three to six months of therapy, followed by minimum of 24 months of maintenance therapy. Treatment usually involves glucocorticoids (GCs) and immunosuppressants, often associated with significant side effects.

For induction, the standard of therapy involves the combination of high dose GCs followed by a steroid tapper and immunosuppressive therapy, primarily cyclophosphamide (CYC) or rituximab (RTX). Other immunosuppressants such as methotrexate (MTX) and mycophenolate mofetil (MMF) may be

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

considered when there is no organ involvement. Plasma exchange (PLEX)[e] is usually reserved for patients with either severe renal impairment or those with diffuse alveolar hemorrhage.

For maintenance of remission, the EULAR/ERA-EDTA recommends a combination of low dose GCs and either azathioprine (AZA), RTX, MTX, or MMF. *(See appendix 10.2 for treatment algorithm in patients with AVV).*

Side effects from immunosuppressive therapy account for the majority of early mortality in AAV, while infection, malignancy, and cardiovascular disease are causes of late mortality. GCs are the cornerstone in the treatment of AVV with both immunosuppressive and anti-inflammatory effects, however, high doses and prolonged duration of GCs may lead to adverse events such as infection, bone fragility, glucose intolerance, hypertension, and weight gain. Immunosuppressants, in general, have a myriad of adverse effects including infection, myelosuppression, hypersensitivity, hepatotoxicity, and malignancy.[8] For example, CYC has significant risks including bone marrow suppression, various organ-system toxicities, malignancies, hepatotoxicity, and embryo-fetal toxicity listed as Warnings and Precautions in its labeling. RTX contains a Boxed Warning for infusion-associated reactions, skin reactions, reactivation of hepatitis B, and progressive multifocal leukoencephalopathy; Warnings and Precautions for RTX include tumor lysis syndrome, infections, various system toxicities, and bowel obstruction and perforations. *(See appendix 10.3 for a brief summary of adverse events associated with commonly used immunosuppressants for AVV.)*

Before starting therapy with immunosuppressants, patients should be screened for hepatitis B virus, hepatitis C virus, HIV, latent tuberculosis, and strongyloides and vaccinated according to latest Centers for Disease Control and Prevention guidelines for immunocompromised patients, including inactivated pneumococcal, influenza, and HBV vaccines, but avoiding live vaccines. Prophylaxis for Pneumocystis Jirovecii pneumonia with trimethoprim/sulfamethoxazole is recommended for all patients receiving induction therapy with GCs and CYC or RTX.

Despite high remission rates with current treatment such as with RTX, recent studies report relapse rates of 5-13% over approximately 2 years which continues to be a concern.[13,14] There is an unmet need for additional therapies, especially those with less toxicities.

4 Benefit Assessment

The clinical reviewer focused primarily on the pivotal phase 3 study (Study CL010_168 [NCT02994927]) which serves as the primary evidence for efficacy and safety of avacopan for the treatment of AVV. The Applicant submitted two additional phase 2 studies (CL002_168 [NCT0136338] and CL003_168, [NCT02222155]) in support of the efficacy of avacopan, however, due to differences in study designs including treatment doses and use of concomitant GCs, the clinical reviewer concluded that they did not provide additional support for the efficacy of avacopan over standard of care nor support for avacopan

[e] PLEX involves taking blood from the patient, separating the plasma, and returning the blood cells to the patient in a substitute fluid. Plasma contains the cells and other substances, such as the protein ANCA, which triggers the damaging immune response.

as a steroid-sparing agent, as proposed by the Applicant. This review will focus on the findings in the phase 3 study

Study CL010_168 (ADVOCATE) is a 60-week, multinational, randomized, double-blind, double-dummy, active-controlled study to evaluate the safety and efficacy of avacopan in inducing and sustaining remission in patients with AAV treated concomitantly with rituximab (RTX) or cyclophosphamide (CYC)/ azathioprine (AZA) in 331 patients. In addition, CL00_168 intends to evaluate whether avacopan could replace a glucocorticoid-tapering regimen used in the treatment of AVV. Patients were stratified based on three factors: 1) receiving IV rituximab, IV cyclophosphamide, or oral cyclophosphamide, 2) Proteinase-3 (PR3) or myeloperoxidase (MPO) ANCA-associated vasculitis, and 3) newly diagnosed or relapsing ANCA-associated vasculitis. Patients were randomized (1:1) to receive avacopan (30 mg twice daily) or matching placebo for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks. Patients who received CYC induction treatment received AZA as maintenance therapy, while patients who received RTX induction treatment did not receive any maintenance therapy. The primary endpoints were the proportion of patients achieving disease remission at Week 26 and the proportion of patients achieving sustained remission at Week 52.[f,g] The primary efficacy analyses were conducted in the modified intention-to-treat (mITT) population, defined as all randomly assigned patients who received at least one dose of trial medication. Endpoints were tested for noninferiority (NI) followed by superiority in a hierarchical testing procedure. The Applicant derived the NI margin of -20% at Week 26 based on meta-analysis of 20 published studies to assess the historical disease remission rates. The demographic and clinical characteristics of the patients at baseline were similar in the two treatment groups. The mean age was 61 years in both groups. Men constituted 59.0% of the avacopan group and 53.7% of the prednisone group. Study CL010_168 met its primary endpoint, demonstrating superiority for sustained remission at Week 52 with avacopan vs. prednisone treatment difference 12.5% for noninferiority and superiority. Noninferiority, but not superiority was demonstrated for remission at Week 26 with avacopan vs. prednisone treatment difference 3.4%. Table 1 provides a summary of the primary endpoints.

[f] Disease remission is defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and no receipt of glucocorticoids for 4 weeks before week 26.

[g] Sustained remission is defined as remission at week 26 and at week 52 and no receipt of glucocorticoids for 4 weeks before week 52.

Table 1. Primary Analysis of Remission at Week 26 and Sustained Remission at Week 52

	Avacopan (N=166)	Prednisone (N=164)	Difference	Non-inferiority p-value	Superiority p-value
Remission at Week 26	120 (72.3%)	115 (70.1%)	3.4%	<0.0001	0.48
95% CI	(64.8, 78.9)	(62.5, 77.0)	(-6.0, 12.8)		
Sustained Remission at Week 52	109 (65.7%)	90 (54.9%)	12.5%	<0.0001	0.0132
95% CI	(57.9, 72.9)	(46.9, 62.7)	(2.6, 22.3)		

Abbreviations: N=the number of patients randomized who received at least one dose of drug; CI=confidence interval.
Counts and percentages relative to N.
Source: Statistical Reviewer.

Secondary endpoints include glucocorticoid-induced toxicity (GTI)[h], BVAS[i] of 0 at Week 4, health-related quality of life (SF-36-v2 and EQ-5D-5L Visual Analogue Scale (VAS) and Index), relapse rates, renal assessments (based on BVAS renal component), and assessment of organ damage (Vasculitis Damage Index [VDI]). As the secondary endpoints were not adjusted for multiplicity, the results are considered exploratory and the uncertainty in the clinical meaningfulness of several of the secondary endpoints makes interpretation of the data unclear. Overall, the review team agreed that avacopan demonstrated superiority for sustained remission at Week 52 and non-inferiority, though not superiority, on remission at Week 26 for its primary endpoints, however, the secondary endpoints provide limited support of a clinically meaningful benefit of avacopan treatment as it is not adjusted for multiplicity.

5 Risk Assessment & Safe-Use Conditions

The safety data for avacopan relied primarily on the phase 3 Study CL010_168. The two phase 2 studies contributed little to the overall safety of avacopan and did not allow for pooling of the safety data. Although the safety population in Study CL010_168 is relatively small (n =239) consisting of all patients who received at least 1 dose of study drug (166 patients exposed to the avacopan arm and 164 patients in the prednisone arm) for up to 52 weeks, the clinical reviewer determined that the baseline demographics and disease characteristics in the safety database reflected most patients with AAV.

A similar proportion of patients in both treatment arms experienced adverse events (AEs), including serious adverse events (SAEs) between prednisone and avacopan treatment arms (45.1% and 42.2%, respectively), treatment emergent adverse events (98.2% and 98.8%, respectively), and adverse events

[h] GTI or Glucocorticoid-induced toxicity is a tool used to quantify toxicity associated with GC use and GC sparing ability of therapies. GTI scores is assessed based on two scores: Cumulative Worsening Score (GTI-CWS) which assesses cumulative GC toxicity and Aggregate Improvement Score (GTI-AIS) which assesses whether therapy is effective at diminishing any GC toxicity over time. Higher scores are reflective of greater toxicity.

[i] BVAS or Birmingham Vasculitis Activity Score is a standardized measure of disease activity, including 57 clinical features, grouped into 9 organ systems plus an "other" category. Scores range from 0 to 63; the higher the score, the more sever the disease.

leading to discontinuation (17.1% and 16.3%, respectively). The most common system organ class (SOC) SAEs were Infections and infestations, 25 (15.2%) in the prednisone arm, and 22 (13.3%) in the avacopan arm. The most common treatment emergent adverse events (TEAEs) reported at > 2% were nausea (20.7% in the prednisone arm and 23.5%, in the avacopan arm), headache (14%, 20.5%), hypertension (17.7%, 18.1%), diarrhea (14.6%, 15.1%), and vomiting (7.9%, 11.4%). The most common SOC in which TEAEs reported in both treatment arms was Infections and infestations (n=113 [68.1%] in the avacopan arm and n=124 [75.6%] in the prednisone arm).

The overall number of deaths was low and similar between treatment arms with four patients who died in the prednisone arm and two patients in the avacopan arm. The clinical reviewer noted that death from worsening GPA and infection is not unexpected in this patient population.

Adverse events of special interests (AESIs) included infections, low white blood cell (WBC) count, hepatotoxicity, and hypersensitivity/angioedema. Infection incidences occurred more frequently in the prednisone arm compared with the avacopan arm. The most common infections were nasopharyngitis, 18.3% and 15.1% (prednisone and avacopan arms, respectively), upper respiratory infection (14.5%, 14.5%), urinary tract infection (14%, 7.2%), pneumonia (6.7%, 6.6%), and sinusitis (7.3%, 6.6%). The proportion of patients with serious infections and opportunistic infections were low and generally similar across treatment arms (avacopan 13.3% and 3.6%; prednisone 15.2% and 6.7%). There was one case of hepatitis B reactivation in the avacopan arm, but the patient also received RTX infusion prior to the event. There were no cases of Neisseria meningitides in the avacopan arm. AEs associated with low WBC count were low and occurred in small numbers and similar across treatment groups, n=31 (18.7%) in the avacopan arm, and n=39 (23.8%) in the prednisone arm.

AESIs of hepatotoxicity and hypersensitivity will be further described in section 5.1 and 5.2, respectively.

5.1 HEPATOTOXICITY

The review team noted imbalances in AEs associated with hepatic abnormalities in the clinical development program and consulted the Drug-induced Liver Injury (DILI) team in the Division of Hepatology and Nutrition (DHN) to evaluate a potential liver safety signal with avacopan observed in the clinical development program. The greatest difference in patients with SAEs (i.e., ≥ 2% difference) was SOC of Hepatobiliary disorders: 3.6% in the avacopan arm over 0.6% in the prednisone arm. Also, only the SOC of hepatobiliary disorders showed ≥ 2% greater incidence of discontinuation: 5 patients in the avacopan arm relative to 0 patients in the prednisone arm. A total of 10 patients receiving avacopan had SAEs related to liver test abnormalities: 9 cases in phase 3 and 1 case in phase 2. Three of the 10 cases were determined to be unlikely related to avacopan. Of the seven remaining cases: 3 were probable, 3 were possible (due to competing diagnosis), and 1 case was highly likely DILI and met criteria for Hy's Law (jaundice and maximum transaminase > 3x upper limit of normal (ULN)).

The DILI team concluded that avacopan can cause liver injury, but the risk of severe injury is unclear due to confounding therapies with potentially hepatotoxic effects.[15] In addition, animal studies involving avacopan did not showed significant liver injury and invitro studies were limited and not informative; therefore, the mechanism of avacopan in liver injury is unclear. The DILI reviewer concedes that the low

number of patients exposed with one possible Hy's Law case is concerning.[j] However, in the case that met Hy's Law criteria, the DILI reviewer considered simvastatin as more likely than avacopan in contributing to the liver abnormalities. Overall, the DILI reviewer could not conclude with confidence of the role of avacopan in this Hy's Law case. In the other cases that are more clearly linked with avacopan, none had jaundice, and all recovered with stopping avacopan.

The DILI reviewer recommends close monitoring of liver tests (e.g., monthly for 6 months) if approved, and to stop avacopan if liver transaminases are over 3 times ULN or baseline without cause, excluding patients with liver disease, and monitoring for HBV infections.

5.2 HYPERSENSITIVITY/ ANGIOEDEMA

Hypersensitivity reactions were few in the phase 3 study and occurred in both treatment arms. However, there was an imbalance in incidences of hypersensitivity and angioedema AEs: two patients (1.2%) in the avacopan group had angioedema (one event was a serious adverse reaction), whereas no patients in the prednisone arm had angioedema. There were 5 additional SAEs of hypersensitivity in the avacopan arm and 3 SAEs in the prednisone arm. Due to the small safety database, no conclusion can be made, and additional studies are needed to further characterize this risk.

6 Expected Postmarket Use

6.1 HEALTHCARE SETTING

Avacopan is proposed for daily oral administration by patients in an outpatient setting to achieve and maintain remission in patients with AAV, although it can be used in an inpatient setting. The primary prescribers for avacopan are rheumatologists, although a multidisciplinary team approach involving other specialists such as neurologists, nephrologists, pulmonologists, dermatologists, and urologists, may be involved depending on the severity and organ system involved. These specialists should be familiar with the risks associated with immunosuppressants (i.e., CYP and RTX) which also have risks of hepatotoxicity and hypersensitivity/ angioedema.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for avacopan beyond routine pharmacovigilance and labeling.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

AVV is a chronic, relapsing multisystem autoimmune disease with high mortality and morbidity, if untreated. Although available therapies help patients attain remission, 5 to 13% patients experience relapses with current treatments. Current available therapies (i.e., GCs, CYC, and RTX) are associated with significant toxicities such as infection, myelosuppression, hepatotoxicity, endocrine and metabolic disruptions, and hypersensitivities which may limit therapeutic options in patients who are intolerant or have inadequate responses to therapies. In addition, the most frequent cause of deaths is therapy-related. There is an unmet need for alternative options, and for therapies with less toxicities.

The Applicant relied on a single phase 3 study, Study CL010_168, to support the effectiveness of avacopan. Study CL010_168 demonstrated superiority for sustained remission at Week 52 (avacopan vs. prednisone treatment difference 12.5%), while only noninferiority for remission at Week 26 (avacopan vs. prednisone treatment difference 3.4%). Secondary endpoints were exploratory and not conclusive as they were not controlled for multiplicity.

The review team presented their concerns regarding the study design, adequacy of efficacy and safety data, and whether the data supported a meaningful benefit for avacopan in the treatment of AAV at the May 6, 2021 AAC.[2] The AAC members had differing interpretations on the clinical meaningfulness of the efficacy and safety data and could not come to a consensus on defining avacopan's role in the treatment of AVV. The AAC voting members split on recommending approval of avacopan for the proposed indication as a treatment for AVV (GPA and MPA) based on the benefit-risk data submitted by the Applicant in the NDA *(see Appendix 10.4 for summary of the voting questions posed to the ACC)*.

Clinical and statistical reviewers

Overall, the clinical and statistical reviewers concluded that the Applicant has not provided confirmatory evidence to support the reliance on a single study to provide substantial evidence of effectiveness for the proposed indication for the treatment of AVV (GPA and MPA) and recommend a Complete Response and the conduct of a second study to better characterize the treatment benefit and benefit-risk balance of avacopan. However, the clinical reviewer acknowledged that the single phase 3 study has met the primary endpoint and that the use of regulatory flexibility for this rare disorder may be considered by other members of the review team for approval of avacopan.

The safety profile in Study CL010_168 is small, with only 166 patients exposed to avacopan, and limited the quantitative analysis of risks. Significant safety concerns associated with avacopan include hepatotoxicity and hypersensitivity/angioedema reactions. Hepatotoxicity is a concern as there were four cases of probable or highly likely drug-induced liver injury with one identified Hy's Law case in the avacopan arm of the phase 3 study. In the Hy's law case, although the DILI reviewer speculated that the latency effect on liver enzymes with simvastatin is more typical than with avacopan, he could not exclude the potential involvement of avacopan. Animal studies did not show safety concerns of hepatotoxicity and the mechanism for hepatotoxicity with avacopan is not known. Other cases of elevated liver enzyme abnormalities did not result in jaundice and had confounding diagnosis, competing therapies with hepatotoxicity risk, and resolved with discontinuation of avacopan. Imbalance

of incidences of hypersensitivity, particularly, angioedema occurred in the phase 3 study with higher incidences in the avacopan group (1.2%) compared to the prednisone group (0%). However, due to the small safety database, no conclusion on this can be made. Labeling discussions are ongoing. The clinical reviewer determined these risks can be adequately managed with labeling and a PMR to further characterize these risks. Labeling will communicate the risk of hepatotoxicity and inform prescribers to avoid using avacopan in certain patient populations (i.e., patients with active, untreated and/ or uncontrolled chronic liver disease and cirrhosis) through Warnings and Precautions (Section 5.1), and informing prescribers to obtain liver test panel prior to treatment initiation in the Dosage and Administration (Section 2.1). The risk of hypersensitivity/ angioedema can be communicated in Warnings and Precautions (Section 5.2). Labeling will also include a contraindication for severe hypersensitivity reactions.

Division Director and Office Director:

The Division Director acknowledges the concerns identified by the clinical and statistical reviewers, but finds that additional considerations ameliorate and outweigh those concerns and sufficient evidence exists to support approval of avacopan as an adjunctive treatment of adult patients with severe active AAV, who are also receiving standard therapy. These considerations are summarized below:

- The phase 3 trial met both the pre-specified primary comparisons: NI in remission at Week 26 and superiority in sustained remission rate at Week 52 based on BVAS remission.
- Though not adjusted for multiplicity, the secondary endpoints include relevant clinical assessments (i.e., relapse rates) which support the clinical activity of avacopan and conclusion of substantial evidence of effectiveness.
- Though optimal use has not been characterized, this does not preclude conclusion of the effectiveness of avacopan in the study population.
- Though the safety data is small, these risks (hepatotoxicity and hypersensitivity) are also seen in other drugs in the therapeutic armamentarium and can be managed through labeling and a PMR to further characterize these safety risks.
- Clinical circumstances may warrant additional flexibility with respect to the acceptability of uncertainties such as an unmet need in patients with severe and life-threatening AVV who do not respond to currently available therapies.

The Office Director concurs with the Division Director's recommendation for approval of avacopan.

9 Conclusion & Recommendations

Based on the available data, this reviewer agrees with DRTM that a REMS is not necessary to ensure the benefits outweigh the risks at this time. Labeling will be used to communicate the risks of hepatotoxicity and hypersensitivity/ angioedema associated with avacopan. A PMR will be required to

further characterize these safety risks, and a PMC to better define the population in which the benefit-risk is favorable.

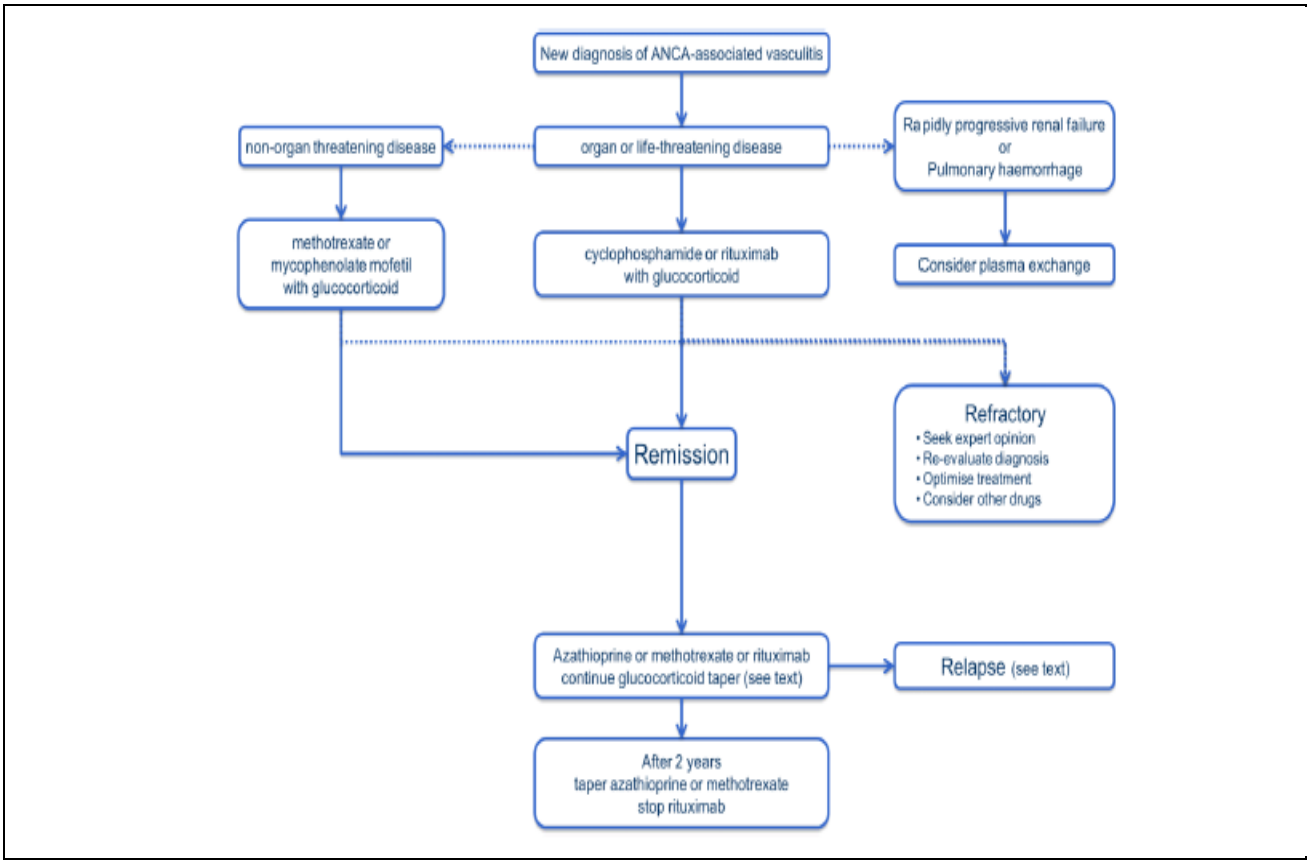
Should DTRM have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. Arthiris Advisory Commitee. FDA and Applicant AAC Briefing Document for avacopan NM, 2021. FDA and Applicant AAC Briefing Document for avacopan, NDA 214487. May 6, 2021.
2. Final Summary Minutes of the ACC Meeting of Avacopan, NDA 214487, dated May 6, 2021.
3. Chee C. NDA 214487 (Avacopan) IR-25 , dated May 18, 2021.
4. ChemoCentryx. Response to the Agnecy's IR 25, dated June 21, 2021.
5. Choi S. NDA 214487 Avacopan, IR-28, dated July 1, 2021.
6. ChemoCentryx. Response to IR 28, dated July 14, 2021.
7. Almaani S, Fussner LA, Brodsky S, Meara AS, Jayne D. ANCA-Associated Vasculitis: An Update. *J Clin Med.* 2021;10(7).
8. Geetha D, Jefferson JA. ANCA-Associated Vasculitis: Core Curriculum 2020. *Am J Kidney Dis.* 2020;75(1):124-137.
9. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis.* 2008;67(7):1004-1010.
10. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis.* 2010;69(6):1036-1043.
11. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis.* 2011;70(3):488-494.
12. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Annals of the Rheumatic Diseases.* 2016;75(9):1583-1594.
13. Smith R, Jayne D, Merkel P. A Randomized, Controlled Trial of Rituximab versus Azathioprine After Induction of Remission with Rituximab for Patients with ANCA-associated Vasculitis and Relapsing Disease. Paper presented at: 2019 ACR/ARP Annual Meeting2019.
14. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. *New England Journal of Medicine.* 2014;371(19):1771-1780.
15. Hayashi P. DHN, DILI Review of Avacopan, NDA 214487, dated June 15, 2021.

10.2 FIGURE 1. MANAGEMENT ALGORITHM OF ANCA-ASSOCIATED VASCULTIS.[12]



Dashed lines indicate alternative or supplementary action to consider

10.3 TABLE 1. COMMONLY USED IMMUNOSUPPRESSANTS FOR AVV

Name (generic)	Formulation(s)	Selected Risk Management Approaches in Labeling
Glucocorticoids (GCs): • Prednisolone • Prednisone	Intravenous (IV) or oral tablets	Warnings/ Precautions: • Infection • Osteoporosis • Diabetes Mellitus • Hypertension • Psychosis/ Depression/ Anxiety/Insomnia
Rituxan (rituximab, [RTX]) Biosimilars available	IV	BW: • Infusion-associated reaction • Mucocutaneous reactions • Hepatitis B virus reactivation, • Progressive multifocal leukoencephalopathy Warnings/ Precautions: • Tumor lysis syndrome • Infections • Cardiac adverse reactions • Renal toxicity • Bowel obstruction and perforation

		• Live virus vaccination – not recommended • Embryo-fetal toxicity
Cytoxan (cyclophosphamide, [CYC])	IV and oral tablets and oral capsule	Warnings/ Precautions: • Bone Marrow Suppression • Urinary and Renal Toxicity – Hemorrhagic cystitis • Cardiotoxicity/pulmonary toxicity • Secondary malignancies • Embryo-fetal toxicity • Hepatotoxicity Contraindications: • Hypersensitivity • Urinary outflow obstruction
Trexall (methotrexate, [MTX])	IV , subcutaneous (SC), and oral tablets	BW: • Embryo-fetal toxicity • Hypersensitivity reactions • Other serious adverse reactions – death, infections, bone marrow suppression, toxicity associated with kidney/ liver/nervous system/ gastrointestinal tract/lung, and skin adverse reactions Warnings/ Precautions: • Embryo-fetal toxicity • Secondary malignancies • Tumor lysis syndrome • Immunization – do not use live vaccines • Infertility Contraindications: • Pregnancy/ breast feeding • Alcoholism/ alcoholic liver disease • Overt or laboratory immunodeficiency syndrome • Pre-existing blood dyscrasias
Imuran (azathioprine, [AZA])	IV and oral tablet	BW: • Malignancy Warnings/ Precautions: • Malignancy – lymphoma • Cytopenia – severe leukopenia, thrombocytopenia, anemias • Serious infections – opportunistic infections/ reactivation of latent infections
Cellcept (mycophenolate mofetil [MMF])	oral capsule, tablet, delay release, and suspension	BW: • Embryo-fetal toxicity • Malignancies • Serious infections Warnings/ Precautions: • Embryo-fetal toxicity • Lymphomas and other malignancies

		• Serious infections – opportunistic infections/ reactivation of latent infections • Blood dyscrasias – neutropenia and Pure Red Cell Aplasia (PRCA)

Source: Information obtained from labeling from Drugs@FDA and Up-to-date

10.4 TABLE 2. SUMMARY OF ARTHRITIS ADVISORY COMMITTEE PANEL DISCUSSION AND VOTING[2]

Panel Questions	Vote	Notes
Do the efficacy data support approval of avacopan for the treatment of adult patients with AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA))?	Yes: 9 No: 9 Abstain: 0	Some committee members wanted confirmatory evidence from another study while others suggested that the drug may be better positioned as a maintenance therapy and recommended a study designed to evaluate this. Some committee members cited the difficulty in conducting studies in this rare disease and that although the results did not demonstrate complete replacement of steroids, the sparing effect was sufficient enough to warrant approval.
Is the safety profile of avacopan adequate to support approval of avacopan for the treatment of adult patients with AAV (GPA and MPA)?	Yes: 10 No: 8 Abstain: 0	A majority of the committee agreed that the safety profile of avacopan is adequate to support approval, but the committee members also recommended post-marketing surveillance. Some members had concern on the small size of the safety population and lack of minority groups, lack of long-term data, and the risks of hepatotoxicity and angioedema.
Is the benefit-risk profile adequate to support approval of avacopan at the proposed dose of 30 mg twice daily for the treatment of adult patients with AAV (GPA and MPA)?	Yes: 10* No: 8 Abstain: 0 *One member answered the question as a hypothetical setting and stated that they would not vote for approval as the data available is not adequate.	Those who voted yes advised on judicious use and guidance for the selection of appropriate patient population for avacopan. Others had concerns about efficacy study design and safety data and the uncertainties regarding GCs and the role of avacopan in the treatment of AVV.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA N NG
10/06/2021 01:44:14 PM

LAURA A ZENDEL
10/06/2021 01:53:01 PM

CYNTHIA L LACIVITA
10/06/2021 01:56:03 PM